MCPRO+ 2.6

Quick Start Guide

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Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

Links to other locations in the current document or to other PDF documents are colored like this: Document Conventions.

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

File name, path, and environment variable syntax is generally given with the UNIX conventions. To obtain the Windows conventions, replace the forward slash / with the backslash \ in path or directory names, and replace the $ at the beginning of an environment variable with a % at each end. For example, `$SCHRODINGER/maestro` becomes `%SCHRODINGER%\maestro`.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Getting Started

The exercises in this document are designed to provide familiarity with some of the basic uses of MCPRO+. Before you begin, you should complete the steps described in the sections below.

1.1 Creating a Working Directory and Copying Files

Before you begin the tutorial exercises you should create a working directory to keep all your input and output files, and then make a copy of the tutorial files.

1. Set the `SCHRODINGER` environment variable to the directory in which Maestro and MCPRO+ are installed:

   csh/tcsh: `setenv SCHRODINGER` *installation_path*

   sh/bash/ksh: `export SCHRODINGER=`*installation_path*

2. Change to a directory in which you have write permission.

   `cd` *mydir*

3. Create a directory by entering the command:

   `mkdir` *directory-name*

4. Copy the files to your working directory (*version* is the 5-digit MCPRO+ version number):

   `cp $SCHRODINGER/mcpro-v`*version*`/tutorial/inputs/*.*` *directory-name*

1.2 Starting Maestro and Setting the Working Directory

Once you have created the working directory you can start Maestro, and if necessary set the Maestro working directory. By default, Maestro writes job files to its working directory. You can change the default in the Preferences panel. If you have changed the default, you should change it back for this tutorial.

1. Change to the desired working directory:

   `cd` *directory-name*

2. Enter the following command:

   ```
   $SCHRODINGER/maestro &
   ```

   The Maestro main window is displayed, and the working directory is Maestro's current working directory. If you are using an existing Maestro session, you can change the directory by choosing Change Directory from the Maestro menu, navigating, to the appropriate directory and clicking Choose.

Minimization

The exercises in this chapter guide you through the minimization of a strained structure in which the amide bond is nonplanar.

2.1 Creating a Model System

The first stage in any MCPRO$^+$ calculation is to create a model system.

1. From the main window, choose Applications > MCPRO+ > Minimization.

   The MCPRO+ Minimization panel opens at the Model System Creation tab and in the Import step.

2. In the Model system section, enter `mini_ms` in the Model system basename text box.

   This name is used to create file names for the job.

3. In the Model system section, select Ligands only.

4. In the Import section, click the Browse button for Ligand structures.

   A file selector opens. The files that you copied to your working directory should be displayed in the Files list. If not, you must navigate to the directory you copied the files to in Section 1.1 on page 1.

5. Select the file `strained.maegz` and click Open.

   The file selector closes, the file name is entered in the Ligand structures text box, and the structure is displayed in the Workspace. If it is not centered, you can click the Fit to screen toolbar button to center it. (This has no effect on the results.)

   

6. Rotate the molecule to view the geometry around the amide bond. (Use the middle mouse button.)

7. In the MCPRO+ Minimization panel, click Constrain.

   The default is to allow the ligands to be fully flexible, which is what we want for this exercise. You do not need to change any settings in this step.

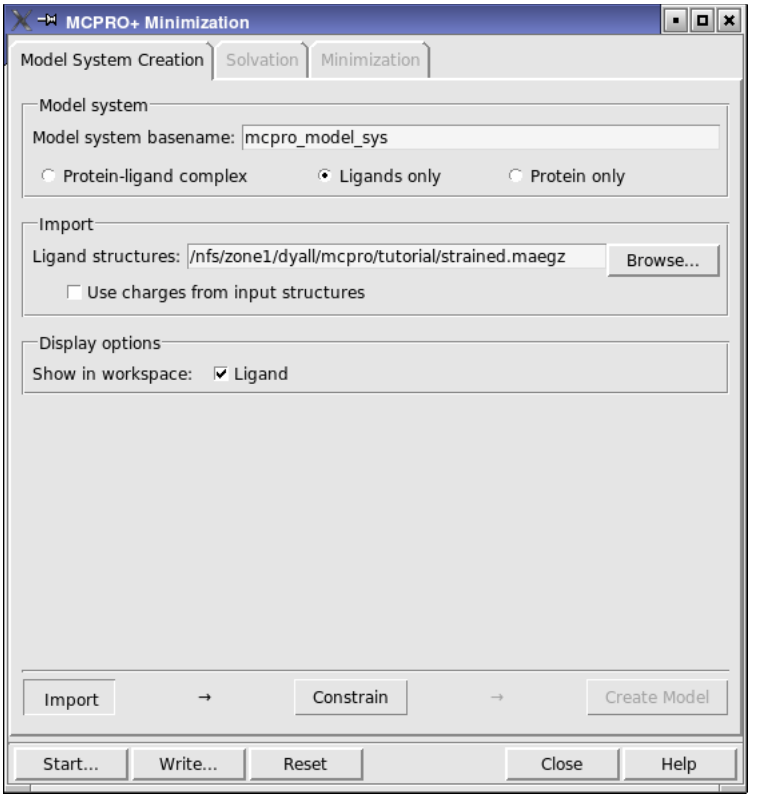

Figure 2.1. The Import step in the MCPRO+ Minimization panel.

8. Click Create Model.

   The job to create the model system is started, and the log file is displayed in the Monitor system creation text area. When it finishes, the message `Model System generated successfully` should appear at the end of the log file.

2.2 Setting Up the Simulation Conditions

In this exercise, you set up the simulation conditions for the minimization. There are only a few options available, so the exercise is short.

1. In the Solvation tab, select Constant dielectric of and ensure that the value in the text box is 78.3.
2. In the Minimization tab, ensure that the Number of optimization cycles is set to 500, and that the Method is set to CONJUG.

2.3 Running the Simulation and Examining the Results

In this exercise, you run the minimization job and examine the results.

1. Click Start.

   The MCPRO+ Start dialog box opens. This job is very quick, so there is no need to run on a remote host, and you can accept the default job name of `mcpro_mini`. This name determines the names of various files.

2. Click Start.

   The job starts, and the Monitor panel opens. The log file is displayed in the File tab. The job finishes almost immediately, and a new structure is displayed in the Workspace.

3. Rotate the molecule to view the geometry around the amide bond.

   Note that the amide bond is now planar.

4. In the Monitor panel, click the Details tab.

5. Select `mcpro_mini.out` in the list of files, and click the File tab.

   The output file is displayed. This is the main text output file, and gives details of the optimization. The energy components are also added to the Maestro output file and displayed as properties in the Project Table.

Creating a Linear Response Model

The exercises in this chapter guide you through the generation of a linear response model from data generated by MCPRO+ simulations. The fitting is done with Strike.

3.1 Creating a Model System

In this exercise, you create a model system that includes both a protein and a set of ligands.

1. From the main window, choose Applications > MCPRO+ > Linear Response.

   The MCPRO+ Linear Response panel opens at the Model System Creation tab and in the Import step.

2. In the Model system section, enter `factorXa_lrm_ms` in the Model system basename text box.

   This name is used to create file names for the job. There is only one choice for the system type, Protein-ligand complex, and it is selected.

3. In the Import section, click the Browse button for Ligand structures.

   A file selector opens. The files that you copied to your working directory should be displayed in the Files list. If not, you must navigate to the directory you copied the files to in Section 1.1 on page 1.

4. Select the file `factorXa_lrm_ligands.maegz` and click Open.

   The file selector closes, the file name is entered in the Ligand structures text box, and the first ligand is displayed in the Workspace. If it is not centered, you can click the Fit to screen toolbar button to center it. (This has no effect on the results.)

   

5. (Optional) From the Draw atoms in Ball & Stick toolbar button menu, choose Molecule, and click on the ligand in the Workspace.

   

   The ligand is displayed in Ball & Stick representation. This will help to distinguish the ligand from the protein in a subsequent step.

6. In the Import section of the MCPRO+ Minimization panel, click the Browse button for Protein structure.
7. Select the file `factorXa_1fjs_protein.maegz` and click Open.

   The file selector closes, the file name is entered in the Protein structures text box, and the protein is displayed in the Workspace along with the first ligand. Note that the ligand is already in the frame of reference of the protein.

   You can change what is displayed in the Workspace by selecting or deselecting the options in the Display options section.
8. Click Chop/Cap.

   The Chop/Cap step is displayed in the panel. For speed, the protein is truncated and the cut bonds are capped with H.
9. Ensure that Keep protein residues within *N* Å of reference ligand is selected, and that the value in the text box is 12.

   These are the default settings, so you should not need to change anything. The protein residues that will be kept are colored yellow in the Workspace, and the residues that will be deleted are colored blue.
10. Click Chop/Cap Protein.

    After a short time, the operation finishes, and the Neutralize button becomes available.
11. Click Neutralize.

    The Neutralize step is displayed. In this step, protons are added or removed to ensure electrical neutrality of the protein-ligand complex. You do not need to change any settings.
12. Click Neutralize Protein.

    After a short time, the operation finishes, and the Constrain button becomes available.
13. Click Constrain.
14. Ensure that, for the protein, Residue sidechains within *N* Å are flexible is selected, and the value in the text box is 8.
15. Ensure that for the cofactors, Fully flexible is selected.

    These are the defaults, so no changes should be needed. The cofactors include the ligand.

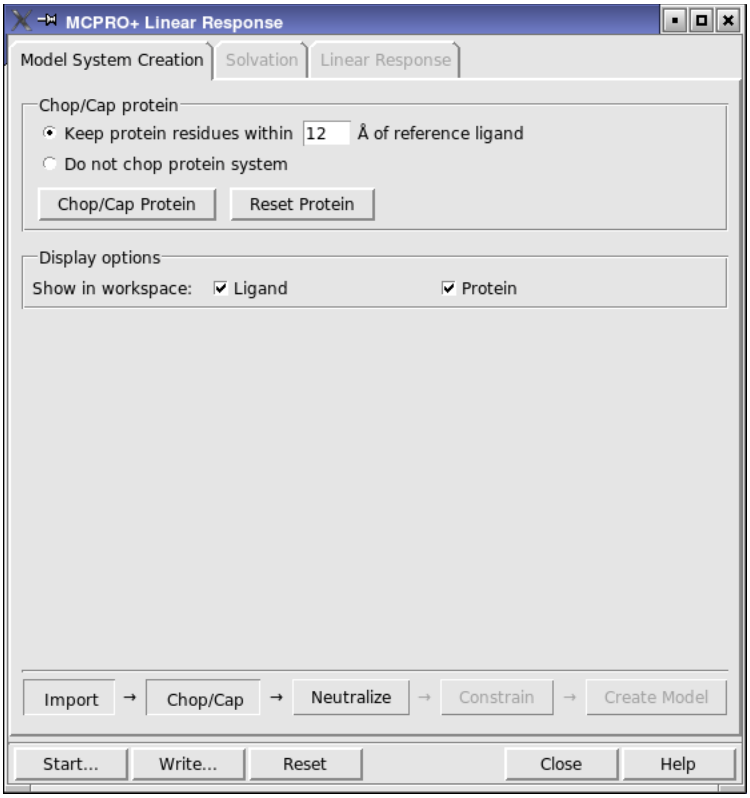

Figure 3.1. The Chop/Cap step in the Model System Creation tab of the MCPRO+ Linear Response panel.

16. Click Create Model.

    The job to create the model system is started, and the log file is displayed in the Monitor system creation text area. When it finishes, the message `Model System generated successfully` should appear at the end of the log file.

3.2 Setting Up the Simulation Conditions

In this exercise, you set up the simulation conditions for the Monte Carlo sampling that is used for the ligand binding energy. The simulations are severely shortened so that the results are obtained quickly. This is only done so that the use of the panel can be demonstrated: it is *not* recommended to use such short simulations routinely.

1. In the Solvation tab, ensure that TIP3P is chosen for the solvent (the default) and that the cap radius is 22 (also the default).

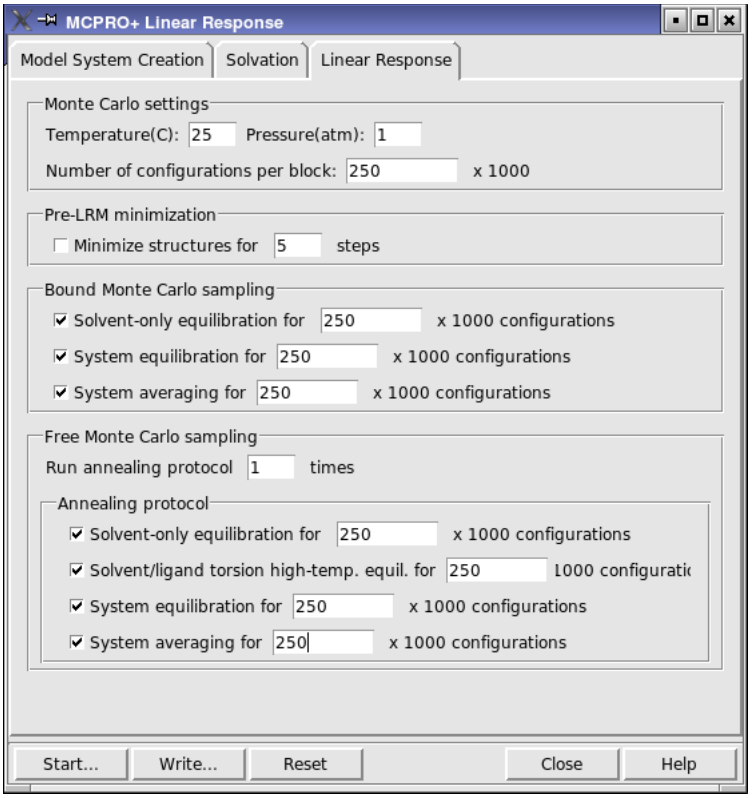

Figure 3.2. The Linear Response tab of the MCPRO+ Linear Response panel.

2. In the Linear Response tab, set the value in all text boxes in the Bound Monte Carlo sampling section to 250.
3. In the Free Monte Carlo sampling section, set the value in the Run annealing protocol N times text box to 1.
4. In the Free Monte Carlo sampling section, in the Annealing protocol subsection, set the value in all text boxes to 250.

3.3 Running the Simulations

In this exercise, you run the simulations. For each of the five ligands, a bound and a free simulation is run, making a total of 10 simulations. A subdirectory is created for each ligand, labeled *jobname_n*, where n is 1 through 5.

1. Click Start.

   The MCPRO+ Start dialog box opens.

2. In the Job section, change the Name to `factorXa_lrm`.

   This name determines the names of various files and the subdirectories that are created for each ligand.

3. Choose a host from the Host option menu.

   The simulations each take about 20 minutes if you run them serially on a 2GHz workstation. If you choose a multiprocessor host, the simulations for each of the ligands can be run simultaneously.

4. Click Start.

   The job starts, and the Monitor panel opens. The log file is displayed in the File tab.

3.4 Creating an Extended Linear Response Model

In this exercise, you create an extended linear response model from the results of the simulation in the previous exercise, using Strike. The structures and associated data were incorporated as an entry group in the Project Table, but the binding free energies need to be imported.

1. Click the Open/Close project table button on the main toolbar.

   

2. In the Project Table, choose Table > Import > Spreadsheet.

   The Import Spreadsheet panel opens.

3. Select the file `factorXa_lrm_dG.txt` and click Open.

   The Choose Import Key dialog box opens.

4. Select title in the File key list.

5. Select Title in the Match to property in Project Table list.

6. Click OK.

   Two new properties should appear in the Project Table, Binding Free Energy (kcal/mol) and Ki(nM), and these properties should have values for the five ligands used in the simulation.

7. In the Project Table, ensure that the five entries in the `factorXa_lrm_out` entry group are selected.

8. From the main window, choose Applications > Strike > Build QSAR Model.

   The Build QSAR Model panel opens.

9. From the Select descriptors to be included in the model list, select EXX-LJ and dHBtot.

   Use control-click to make the selection. These two descriptors will be the independent descriptors.

10. From the Regression method option menu, choose Multiple Linear Regression.

11. Select y-intercept through origin.

12. Click the Choose button for the Activity property.

    The Choose Activity Property dialog box opens. This dialog box presents a list of Maestro properties, from which you can choose one property.

13. Select Binding Free Energy (kcal/mol) and click OK.

    This descriptor is the dependent descriptor.

14. Click Start.

    The Start dialog box opens.

15. Name the job `factorXa_lrm_fit`, and click Start.

When the job finishes, the results are returned to the Results table of the Build QSAR Model panel. This model is based on a very short simulation, whose results are likely to be noisy and show poor statistics. In general good models should show

- a small standard deviation
- a large R^2
- a large F value
- $P < 0.05$
- good leave-n-out cross-validation results
- physically meaningful descriptors
- a low R^2 from randomization tests

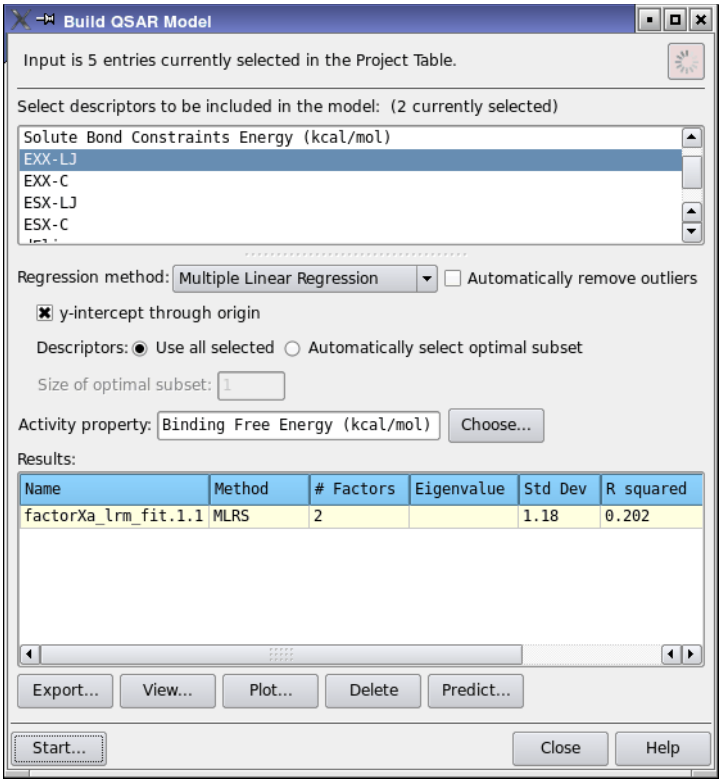

Figure 3.3. The Build QSAR Model panel.

Instead of using Strike, fitting can be done in a spreadsheet program, by exporting the data as a CSV file, which you can do from the Table menu in the Project Table panel.

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Maestro menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel, or press F1. The help topic is displayed in your browser.
- For other information in the online help, open the default help topic by choosing Online Help from the Help menu on the main menu bar or by pressing CTRL+H. This topic is displayed in your browser. You can navigate to topics in the navigation bar.

The Help menu also provides access to the manuals (including a full text search), the FAQ pages, the New Features pages, and several other topics.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *Maestro Overview*, for an overview of the main features of Maestro
- *Maestro Tutorial*, for a tutorial introduction to basic Maestro features
- *MCPRO+ User Manual*, for detailed information on using MCPRO$^+$
- MCPRO$^+$ Frequently Asked Questions pages, at https://www.schrodinger.com/MCPRO_FAQ.html

- Known Issues pages, available on the Support Center.

The manuals are also available in PDF format from the Schrödinger Support Center. Local copies of the FAQs and Known Issues pages can be viewed by opening the file `Suite_2009_Index.html`, which is in the `docs` directory of the software installation, and following the links to the relevant index pages.

Information on available scripts can be found on the Script Center. Information on available software updates can be obtained by choosing Check for Updates from the Maestro menu.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information:

- All relevant user input and machine output
- MCPRO$^+$ purchaser (company, research institution, or individual)
- Primary MCPRO$^+$ user
- Computer platform type
- Operating system with version number
- MCPRO$^+$ version number
- Maestro version number
- mmshare version number

On UNIX you can obtain the machine and system information listed above by entering the following command at a shell prompt:

```
$SCHRODINGER/utilities/postmortem
```

This command generates a file named *username*`-`*host*`-schrodinger.tar.gz`, which you should send to help@schrodinger.com. If you have a job that failed, enter the following command:

```
$SCHRODINGER/utilities/postmortem jobid
```

where *jobid* is the job ID of the failed job, which you can find in the Monitor panel. This command archives job information as well as the machine and system information, and

includes input and output files (but not structure files). If you have sensitive data in the job launch directory, you should move those files to another location first. The archive is named *jobid*`-archive.tar.gz`, and should be sent to help@schrodinger.comIf Maestro fails, an error report that contains the relevant information is written to the current working directory. The report is named `maestro_error.txt`, and should be sent to help@schrodinger.com. A message giving the location of this file is written to the terminal window.

More information on the `postmortem` command can be found in Appendix A of the *Job Control Guide*.

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